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(54) Title: IN VITRO CELL-BASED METHODS FOR BIOLOGICAL VALIDATION AND PHARMACOLOGICAL SCREENING OF CHEMICAL ENTITIES AND BIOLOGICALS

(57) Abstract: This patent describes a novel *in vitro* cell-based method for biological validation and pharmacological screening of drugs, new chemical entities (NCEs) and biologics, which is predictive of *in vivo* testing for efficacy and adverse events in patients, as occurs in clinical trials. The same method can be used to create an *in vitro* cell-based assay to identify the 'right' marketed medication for the 'right patient' (personalized medicine), and to identify responders/non-responders in ongoing clinical trials with NCEs. In addition this approach can be used to identify new indications for existing medicines and new indications for NCEs that were unsuccessful in their intended uses.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/43726A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C12Q1/68 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIRANO TOSHIHIKO ET AL: "Clinical significance of glucocorticoid pharmacodynamics assessed by antilymphocyte action in kidney transplantation: Marked difference between prednisolone and methylprednisolone." TRANSPLANTATION (BALTIMORE), vol. 57, no. 9, 1994, pages 1341-1348, XP001121774 ISSN: 0041-1337 page 1341 -page 1344 -----	1-7, 25-28, 32
X	WO 96 35948 A (LANDSTINGET I OESTERGOETLAND ;HAAKANSSON LEIF (SE)) 14 November 1996 (1996-11-14) page 8 -page 12; figures 6,9; example 3 -----	1-7, 25-28, 32

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search  13 January 2003	Date of mailing of the international search report  12.05.03
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Friedrich, C

## INTERNATIONAL SEARCH REPORT

national application No.  
PCT/US 01/43726

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7, 25-28, 32 (all in part)

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

1. Claims: 1-7, 25-28, 32 (all in part)

PBMC based method to predict success or failure of in vivo treatment with chemical entities relying on cellular responses.

2. Claims: 4, 10, 15-19, 20-24, 29 (all in part)

Method to increase sensitivity of PBMC to chemical entities by transfection with a zinc finger protein.

3. Claims: 8-14 , 15-19, 20-24, and 29

Method to predict in vivo response to treatment with a chemical entity based on PBMC gene expression analysis.

4. Claim : 30

PBMC based method to predict success or failure of in vivo treatment with chemical entities relying on gene expression detected on microarrays.

5. Claim : 31

PBMC based method to predict success or failure of in vivo treatment with chemical entities relying on gene expression detected on microbeads.

## INTERNATIONAL SEARCH REPORT

## Information on patent family members

International Application No

PCT/US 01/43726

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9635948 A	14-11-1996	AT 214160 T CA 2215630 A DE 69619667 D DE 69619667 T EP 0824695 A JP 11504714 T US 6242202 B	15-03-2002 14-11-1996 11-04-2002 31-10-2002 25-02-1998 27-04-1999 05-06-2001